Evidence-Based Management of Bullous Pemphigoid

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KEYWORDS

• Bullous pemhigoid • Autoimmune bullous disease
• Topical corticosteroids • Systemic corticosteroids

Bullous pemphigoid (BP) is the most common autoimmune bullous disease, preferentially affecting the elderly.[1,2] It is characterized by generalized pruritus with subsequent subepidermal bullous formation as well as the detection of autoantibodies against the BP180 (BPAG2, type XVIII collagen) and BP230 (BPAg1-e) antigens. Multiple treatments have been used, though evidence supporting their use is deficient because of a paucity of adequate clinical trials. This shortcoming is partly due to the low prevalence and heterogeneous nature of the disease, and differing study designs with small numbers of patients.

Elderly patients are more likely to have multiple comorbidities and be susceptible to changes in medications than other populations. As a result, adverse effects and potential drug interactions should be considered when treating BP. It is therefore important to provide a review of the evidence supporting the various treatments for BP, so that clinicians can select the best and most efficient medication for their patients. Each treatment regimen must be individualized according to the severity of disease, comorbidities, and patients' expectations. Furthermore, the physician's personal experience and drug availability also affect the final choice. Clinical manifestations, epidemiology, and pathogenesis have been reviewed in the previous issue of *Dermatologic Clinics*. This article focuses on the adaptation of the evidence-based trials in BP to a practical system of managing BP. The authors consider the treatment approach under 3 headings: (1) the context, (2) the treatments, and (3) the morbidity and mortality.

THE CONTEXT OF THE TREATMENT

The average age of presentation in BP is usually between 75 and 85 years,[3–6] with many comorbidities, and hence there is a need to be cautious with treatments.[7] BP patients are often either in nursing homes or are already dependent on relatives for care. Three independent case-control studies have shown that there is a high risk of prior neurologic problem 5 to 10 years before the onset of BP.[8–10] Hence, when treating patients with BP, consideration should be given to 3 important factors that may increase the morbidity and/or mortality of the treatment: (1) patient age, (2) underlying diagnosis such as diabetes mellitus,

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hypertension, or cardiovascular disease, and (3) the multitude of side effects associated with the use of high doses of systemic corticosteroids. The drugs given to this population need to be tempered with the understanding that they could interfere with other medical problems and will require the assistance of third parties to administer it in most cases. The first consideration is to do no more good than harm to this vulnerable group of patients, no matter how effective a particular treatment may appear in trials perhaps involving healthier patients.

THE EVIDENCE FOR THE TREATMENTS

The treatments under discussion include corticosteroids (oral and topical) and steroid-sparing agents. The latter include, among others, azathioprine, mycophenolate mofetil (MMF), tetracyclines with or without nicotinamide, dapsone, cyclophosphamide, intravenous immunoglobulin (IVIG), plasmapheresis, and rituximab. These agents and their overall important treatment questions are discussed.

THE SAFETY OF THE TREATMENTS

As each type of treatment is discussed, the drawbacks of each type of treatment are mentioned, this being particularly important in the context of the elderly population with BP.

QUESTIONS THAT REMAIN TO BE ANSWERED

There are 3 main questions remaining to be answered in BP management:

1. What is the optimal dose and route of administration of corticosteroids for newly diagnosed BP?
2. What population of BP patients should be treated with oral versus topical corticosteroids versus steroid-sparing drugs?
3. Are steroid-sparing drugs safe and effective?

The goal of treatment in BP is to arrest disease progression, reduce itch, and rapidly stimulate healing of blisters. Quick and efficient therapy is important, as extensive disease with delayed healing is also prone to infection and may require antibiotic coverage and, in severe cases, hospitalization. Patients may present at various stages of clinical severity, due to a delay in diagnosis (particularly in types presenting with diffuse pruritus only, urticarial or eczematous BP before the blistering develops).

A recent Cochrane review of the 7 randomized controlled trials (RCTs) concluded the following: (1) very potent topical steroids are effective and safe treatments for BP; (2) their use in extensive disease may be limited by side effects and practical factors; (3) starting doses of prednisolone greater than 0.75 mg/kg/d do not seem to give additional benefit in disease control and they may reduce the incidence and severity of adverse reactions; (4) the effectiveness of the addition of plasma exchange or azathioprine to corticosteroids has not been established; and (5) combination treatment with tetracycline and nicotinamide may be useful, but this needs further validation.[10] A summary of these trials is given in **Table 1**.

For question (1), the optimal starting dose for oral prednisone/prednisolone should be no higher than 0.75 mg/kg/d, as there was no significant difference in resolution of blistering between days 21 and 50 using this dose in comparison with 1.25 mg/kg/d.[11] The formulation of steroid does not seem to matter, because Dreno's[12] study comparing methylprednisolone versus prednisolone found no significant difference.

The type of steroid, dosage, and duration of therapy varies among clinicians. A survey of German dermatologists[13] found that 53% of the hospitals prescribed less than 1 mg/kg/d as the initial dose whereas the remainder (47%) used the higher dose of 1 to 2 mg/kg/d. About one-third of hospitals aim to maintain patients on less than 7.5 mg/d prednisone (or equivalent), whereas others prefer tapering until prednisone can be stopped. The effectiveness of prednisone is related to the number of blisters before initiation of treatment, and it has been suggested that they should not be discontinued if response is not observed within a certain timeframe.[14] Duration of treatment or an increased dose may be required for extensive disease to respond. However, systemic corticosteroids are responsible for multiple adverse effects, and can be detrimental and potentially fatal in the elderly.[15]

Although systemic steroids have conventionally been used as the mainstay of treatment, their long-term use increases the risk of steroid-associated side effects (**Box 1**)[16] and should therefore be minimized or tapered once clinical improvement is detected. The use of topical corticosteroids has been evaluated as a possible way to avoid systemic corticosteroids in some patients with BP.

A landmark study of bullous diseases by a French group randomized BP patients to topical versus oral steroids,[17] and found that topical clobetasol propionate (40 g/d) was associated with improved overall survival ($P = .02$) and fewer severe adverse effects ($P = .006$) than oral prednisone in patients with extensive BP (defined as presence of more than 10 new blisters per day on 3 consecutive days). In severe BP, survival in the oral prednisone group at 1 year was 58% and in the topical steroid group was 76%, and severe complications were more common in the oral (54%) than in the topical (29%) treatment groups. There was no difference in disease control